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Molecular co-crystals of 2-aminothiazole derivatives

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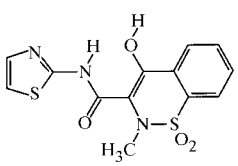
Abstract

A series of molecular adducts of 2-aminothiazole derivatives – 2-aminothiazole, 2-amino-2-thiazoline and 2-aminobenzothiazole with the carboxylic-acid-substituted heterocyclics indole-2-carboxylic acid, *N*-methylpyrrole-2-carboxylic acid and thiophene-2-carboxylic acid – have been prepared and characterized using X-ray powder diffraction and in five cases by single-crystal X-ray diffraction methods. These five compounds are the adducts of 2-amino-2-thiazolium with indole-2-carboxylate $[(C_3H_7N_2S)^+(C_9H_6NO_2)^-]$, and *N*-methylpyrrole-2-carboxylate $[(C_3H_7N_2S)^+(C_6H_6NO_2)^-]$, 2-aminobenzothiazolium with indole-2-carboxylate $[(C_7H_7N_2S)^+(C_9H_6NO_2)^-]$, *N*-methylpyrrole-2-carboxylate $[(C_7H_7N_2S)^+(C_6H_6NO_2)^-]$ and thiophene-2-carboxylate $[(C_7H_7N_2S)^+(C_5H_3O_2S)^-]$. All complexes involve proton transfer, as indicated by IR spectroscopy, while the five crystal structures display similar hydrogen-bonding patterns with the dominant interaction being an $R_2^2(8)$ graph set dimer association between carboxylate groups and the amine/heterocyclic nitrogen sites. Futhermore, in each case a subsiduary interaction between an amino proton and a carboxylate oxygen completes a linear hydrogen-bonded chain. In addition to this, the indole-2-carboxylate molecules in the adduct structure with 2-amino-2-thiazolium form associated dimers which add to the hydrogen-bonding network.

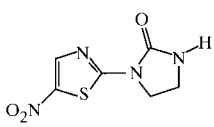
1. Introduction

Aminothiazoles have many applications in both human and veterinary medicine (Metzger, 1979). The antiviral, antimicrobial and bactericidal properties of 2-amino-thiazoles and 2-amino-4-thiazolines have been extensively studied. These compounds exhibit marked antitrichonomal activity, which has been measured quantitatively by the Hansch approach (Kutter *et al.*, 1972). Their anti-inflammatory activity (Nagatomi & Ando, 1984) and antiparasitic action has led to two classes of these compounds being given trade names: Sudoxicam and Nitridazole (or Ambilhar). The ability of aminothiazoles to form proton-transfer complexes was realized when investigations were carried out in order to gain structural information enabling a study of the effect of the amino group on the activity of 2-aminohistamine derivatives (Nardelli *et al.*, 1987). In all of the compounds studied a cation was formed by the protonation of the ring N atom which, coupled with π-conjugation, makes the juxta-NH_2 group coplanar with the ring. It was found that the biological properties of 2-aminohistamine could be ascribed to the existence, in the H_2-receptor, of a hydrophilic area which was suitable for receiving the juxta-nuclear NH_2, rather than for a direct involvement of this group in the amidinic activation. Other studies have shown catalase and cytosolic epoxide hydrolase activity inhibited by hydroxylated metabolites of 2-amino-4,5-diphenylthiazole (Guenthner *et al.*, 1989), while 2-amino-2-thiazoline is a potential inducer of the reverse transformation of tumour cells (Kubiak & Glowiak, 1984; Kubiak *et al.*, 1983). The mechanism of anticancer action depends on another important property exhibited by aminothiazoles – metal–ligand binding. It has been suggested that the aminothiazole binding sites for metal centres (*i.e.* Zn, Mn, Ni and Cu) in biological systems are mainly the N atoms. The coordination of 2-aminothiazole to the M^{II} ions of Co (Raper *et al.*, 1981, 1984), Zn (Macicek & Davarski, 1993) and Cu (Antsyshkina *et al.*, 1989; Wang *et al.*, 1995) has been studied, and heterocyclic nitrogen-bonded, rather than sulfur-bonded, complexes are observed.

Sudoxicam



Nitridazole



A large number of 2-aminothiazole derivatives have pronounced fungicidal activity (Giri & Shukla, 1966). 2-Bromo-4-aminothiazole derivatives show biological activity against fungus, brown root and plant countail, while 2-aminothiazole has been tested for fungistatic activity on wheat. Another important use, if confirmed, is that of a nitrification inhibitor (Sampei, 1972). 2-Aminothiazole derivatives are also used as dyeing compounds. Their importance lies in their performance

on acetate fibres where they have an excellent fastness to gas fumes and produce bright blue shades. 2-Aminothiazole is an effective brightener used in copper-plating baths; it inhibits the corrosion of mild steels as well as copper alloys (Al-Hajjar & Al-Kharafi, 1988; Desai *et al.*, 1975) and it also improves the adhesive properties of wood to wood glue. A related compound, 2-amino-4-phenylthiazole hydrobromide monohydrate, reduces the corrosion rate of mild steel in 0.1 *M* HCl (Form *et al.*, 1974). However, after such an extensive range of studies into the properties and applications of 2-aminothiazoles, there are only eight previously characterized X-ray structures of organic adducts of this compound and its derivatives. These include 2-aminothiazolium trichloroacetate (Kuz'mina & Struchkov, 1984), *N*,*N*-dimethyl-2-(2-amino-5-thiazolyl)ethylamine dipicrate (Nardelli *et al.*, 1987), (−)-2,6-diamino-4,5,6,7-tetrahydrobenzothiazolium (L)-(+)-tartrate trihydrate (Schneider & Mierau, 1987), 2-aminobenzothiazole hexamethylphosphoramide (Armstrong, Bennett *et al.*, 1992), 2-aminobenzothiazole *N*,*N*-dimethylpropylene-urea (Armstrong, Davidson *et al.*, 1992), 2-aminobenzothiazolium 3,5-dinitrobenzoate hydrate, 2-aminobenzothiazole 3-aminobenzoic acid and 2-amino-2-thiazolinium 2-aminobenzoate (Lynch, Smith *et al.*, 1998). Of these structures, five contain adduct

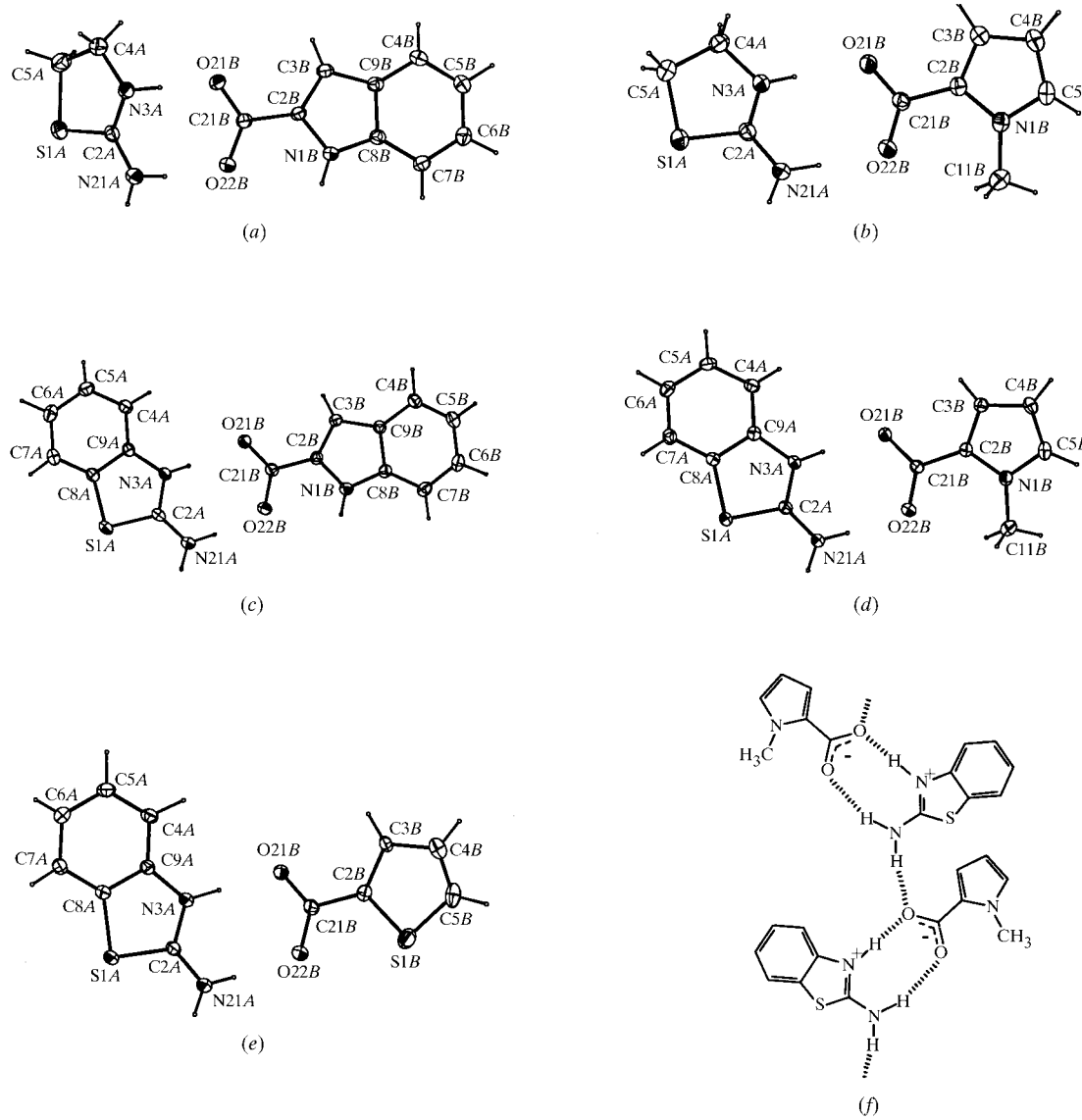
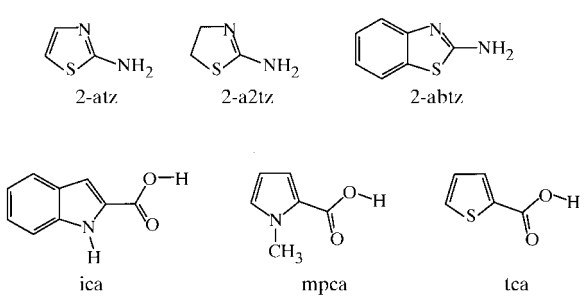


Fig. 1. Atom-numbering schemes and views of the $R_2^2(8)$ associations for the molecular aggregates in (*a*) [(2-a2tz)(ica)] (4), (*b*) [(2-a2tz)(mpca)] (5), (*c*) [(2-abtz)(ica)] (7), (*d*) [(2-abtz)(mpca)] (8) and (*e*) [(2-abtz)(tca)] (9). Displacement ellipsoids are drawn at the 20% probability level. (*f*) [(2-abtz)(mpca)] (8), demonstrating the extended hydrogen-bonding network present in all structures.

components with substituted carboxylic acid groups. When adducted with a carboxylic acid, 2-aminothiazole derivatives may form dimers of uncharged molecules across the 2-amino/heterocyclic N site, shown below. Only the 2-aminobenzothiazole 3-aminobenzoic acid adduct structure displays this form; the remaining four carboxylic-acid-based structures, the dipicrate structure, eight other non-bonding metal structures (Antolini *et al.*, 1988; Fernandez *et al.*, 1987, 1996; Kubiak & Glowiak, 1984; Kubiak *et al.*, 1983) and two hydrohalide structures (Form *et al.*, 1974; Rybinov *et al.*, 1989) involve proton transfer to the heterocyclic nitrogen. Thus far no systematic study of the structural aspects of adducts of 2-aminothiazole derivatives with carboxylic acids has been performed. The parent structures of 2-aminothiazole (Caranoni & Reboul, 1982) and 2-amino-4-nitrobenzothiazole (Lokaj *et al.*, 1996) have been previously reported.

Three aminothiazole derivatives, 2-aminothiazole (2-atz), 2-amino-2-thiazoline (2-a2tz) and 2-aminobenzothiazole (2-abtz), and three heterocyclic carboxylic acids, indole-2-carboxylic acid (ica), *N*-methylpyrrole-2-carboxylic acid (mpca) and thiophene-2-carboxylic acid (tca), were used in the preparation of adducts and are listed in Table 1. All complexes were characterized using the melting point, IR spectroscopy and X-ray powder diffraction techniques. The structures of compounds (4), (5) and (7)–(9) have been determined by single-crystal X-ray diffraction.



2. Experimental

2.1. *Preparations*

For complexes (1)–(9) all preparations involved refluxing equimolar amounts (2.2 mmol) of the component molecules for 20 min at ~353 K in 40 cm^3 of 95% ethanol, the product being subsequently obtained by the total evaporation of the solvent at room temperature; experimental results are listed in Table 1. Adduct formation was identified in each case by X-ray powder diffraction techniques by using a Philips PW1700 System diffractometer (Cu $K\alpha$ X-radiation). IR spectra were recorded as pressed discs in KBr on a Nicolet 205 FT-IR spectrometer.

2.2. *Data collection, structure solution and refinement*

Details of cell data, data collection and refinement are summarized in Table 2. In all cases, cell parameters were determined from 25 reflections collected across a θ range 6–14°. Negligible change (<1%) in the intensities of three standards monitored every 200 reflections throughout the respective data-collection periods indicated no significant crystal decomposition. Data were corrected for Lorentz and polarization effects. All structures were solved by direct methods and refined using *SHELX*97 (Sheldrick, 1997). H atoms were mostly located by difference methods and both positional and thermal parameters were refined, although the 5-CH_2 (2-a2tz) and *N*-CH_3 (mpca) protons in (5) and all three tca protons in (9) were included in their respective refinements at calculated positions as riding models. Final fractional coordinates are presented in Table 3. *PLATON*94 (Spek, 1990) was used to calculate the hydrogen-bonding interactions listed in Table 4.†

3. Results and discussion

3.1. *Molecular structures of [(2-a2tz)(ica)] (4), [(2-a2tz)(mpca)] (5), [(2-abtz)(ica)] (7), [(2-abtz)(mpca)] (8) and [(2-abtz)(tca)] (9)*

The 1:1 adducts all display similar packing arrangements and are all proton-transfer complexes (Fig. 1). As expected for these systems, the intermolecular associations involve the formation of hydrogen-bonded cyclic dimers [graph set $R_2^2(8)$ (Etter, 1990)] *via* the N21 and N3 sites of the aminothiazolium molecules and the complementary carboxylate groups (distances and angles involved in the hydrogen-bonding interactions are listed in Table 4). In each case the packing network is completed by an additional hydrogen-bonding interaction which consists of an association between the second N21 proton and an adjacent carboxylate O atom (*cf.* Table 4), thus forming hydrogen-bonded polymeric chains throughout the crystal lattice, as shown in Fig. 1 for (8). However, in the structure of (4) an additional indole N—H interaction is observed where the ica molecules form dimers through a single interaction between the indole N—H and an adjacent carboxylate O atom [N1*B*—H1*B*—O22*B* 2.845 (3) Å, ∠N—H—O 156 (3)° ($-x$, $-y$, $-z$)], as shown in Fig. 2.‡ Because of this, the dihedral angle between the plane of S1*A*, C2*A*,

† Supplementary data for this paper are available from the IUCr electronic archives (Reference: HA0177). Services for accessing these data are described at the back of the journal.

‡ This configuration for ica is also seen in the 1:1 adduct with 5-nitroquinoline (Lynch, Mistry *et al.*, 1998); comparative N—H—O distances and angles for two unique ica molecules are 3.001 (6) Å, ∠ 162 (3)° and 2.968 (6) Å, ∠149 (3)°.

Table 1. *Experimental results for compounds (1)–(9)*

Compounds (1)–(3), (6) and (8) were collected as off-white powders. For 2-atz, *d* (*I*/*I*$_0$) 3.62 (100%), 4.22 (75), 4.78 (40), 3.90 (40), 4.80 (35), 3.03 (25), 2.76 (25), 2.70 (25) Å. For 2-a2tz, *d* (*I*/*I*$_0$) 3.75 (100%), 4.99 (90), 3.79 (65), 5.26 (55), 3.65 (45), 2.67 (45), 4.61 (40), 5.43 (35) Å. For 2-abtz, *d* (*I*/*I*$_0$) 14.43 (100%), 7.24 (80), 2.91 (12), 3.63 (7), 5.26 (5), 3.85 (5), 3.29 (5), 3.57 (3) Å. For ica, *d* (*I*/*I*$_0$) 14.72 (100%), 7.46 (42), 4.89 (30), 3.40 (23), 3.26 (23), 5.92 (22), 5.42 (17), 3.24 (17) Å. For mpca, *d* (*I*/*I*$_0$) 5.15 (100%), 5.19 (91), 10.14 (42), 5.09 (38), 5.23 (30), 3.96 (26), 3.99 (23), 3.40 (16) Å. For tca, *d* (*I*/*I*$_0$) 5.23 (100%), 3.40 (60), 5.64 (30), 4.59 (30), 3.12 (30), 4.88 (20), 2.85 (20), 3.63 (12) Å.

Compound	M.p. (K)	C, H, N analysis	X-ray powder diffraction data: *d* Å (*I*/*I*$_0$)
[(2-atz)(ica)] (1)	387–390	C, 55.1; H, 4.2; N, 16.0% $C_{12}H_{11}N_3O_2S$ requires C, 55.2; H, 4.2; N, 16.1%	5.11 (100%), 5.10 (91), 4.23 (89), 4.81 (60), 4.13 (55), 4.73 (54), 4.31 (48), 5.14 (46)
[(2-atz)(mpca)] (2)	352.5–353.5	C, 47.9; H, 4.7; N, 18.8% $C_9H_{11}N_3O_2S$ requires C, 48.0; H, 4.9; N, 18.7%	6.12 (100%), 3.85 (57), 3.17 (25), 3.44 (17), 3.77 (15), 4.79 (14), 7.53 (13), 6.28 (12)
[(2-atz)(tca)] (3)	372–376	C, 42.0; H, 3.5; N, 12.4% $C_8H_8N_2O_2S_2$ requires C, 42.1; H, 3.5; N, 12.3%	3.85 (100%), 5.47 (69), 5.10 (33), 3.74 (25), 3.35 (19), 5.92 (15), 3.06 (14), 3.29 (13)
[(2-a2tz)(ica)] (4)	426–428	C, 54.9; H, 5.1; N, 16.0% $C_{12}H_{13}N_3O_2S$ requires C, 54.7; H, 5.0; N, 16.0%	4.00 (100%), 5.25 (84), 3.98 (71), 3.77 (47), 3.66 (35), 3.68 (33), 3.54 (32), 3.94 (31)
[(2-a2tz)(mpca)] (5)	433–435	C, 47.8; H, 5.9; N, 18.5% $C_9H_{13}N_3O_2S$ requires C, 47.6; H, 5.8; N, 18.5%	4.35 (100%), 3.74 (61), 3.73 (59), 4.48 (56), 4.68 (46), 5.41 (45), 4.85 (32), 4.83 (31)
[(2-a2tz)(tca)] (6)	437–440	C, 41.8; H, 4.3; N, 12.0% $C_8H_{10}N_2O_2S_2$ requires C, 41.7; H, 4.4; N, 12.2%	4.36 (100%), 3.33 (71), 4.99 (41), 5.73 (27), 4.22 (14), 3.36 (11), 5.80 (11), 11.43 (10)
[(2-abtz)(ica)] (7)	443.5–446	C, 61.8; H, 4.2; N, 13.4% $C_{16}H_{13}N_3O_2S$ requires C, 61.7; H, 4.2; N, 13.5%	3.37 (100%), 9.70 (78), 4.44 (61), 4.51 (61), 3.77 (59), 3.58 (39), 5.83 (36), 5.27 (35)
[(2-abtz)(mpca)] (8)	377–380	C, 56.9; H, 4.7; N, 15.2% $C_{13}H_{13}N_3O_2S$ requires C, 56.7; H, 4.8; N, 15.3%	9.82 (100%), 4.92 (44), 3.62 (42), 4.21 (26), 10.22 (19), 14.47 (18), 7.25 (13), 4.55 (12)
[(2-abtz)(tca)] (9)	415–420	C, 51.8; H, 3.5; N, 10.0% $C_{12}H_{10}N_2O_2S_2$ requires C, 51.8; H, 3.6; N, 10.1%	3.62 (100%), 5.64 (70), 5.01 (34), 4.19 (28), 9.33 (26), 4.48 (26), 3.35 (23), 4.21 (20)

N21*A* and N3*A* in the aminothiazole ring (*B*), and the indole plane is increased [$\angle A-B$ 57.3 (2)°] so as to allow the indole moieties to associate. For the other compounds the angle between associated *A* and *B* molecules is <30°. In the structure of (4) the torsion angle S1*A*—C5*A*—C4*A*—N3*A* (for 2-a2tz) is 10.8 (2)°. For (5), two C—H—O interactions exist from both a pyrrole C—H and a 2-a2tz alkyl C—H to the same carboxylate O atom [C4*B*—H4*B*—O22*B* 3.384 (3) Å, ∠C—H—O 170 (3)° ($\frac{1}{2}+x, \frac{1}{2}-y, z$); C4*A*—H41*A*—O22*B* 3.290 (3) Å, ∠C—H—O 132 (3)° ($-x, \frac{1}{2}+y, \frac{1}{2}-z$)]. Similarly, for (5), the torsion angle S1*A*—C5*A*—C4*A*—N3*A* is −5.58 (2)°. For (7), the indole N—H does not contribute to the hydrogen-bonding network. A possible reason for this is the presence of a single C—H—O interaction from an aromatic C—H to the carboxylate O atom [C7*B*—H7*B*—O22*B* 3.261 (5) Å, ∠C—H—O 130 (3)° ($2-x, -y, 2-z$)] adjacent to the indole N—H, thus sterically hindering any potential associations. In (9) a single C—H—O interaction exists between a benzene proton on the 2-abtz ring and O22*B* [C7*A*—H7*A*—O22*B* 3.233 (5) Å, ∠C—H—O 146 (3)° ($-x, -\frac{1}{2}+y, \frac{3}{2}-z$)].

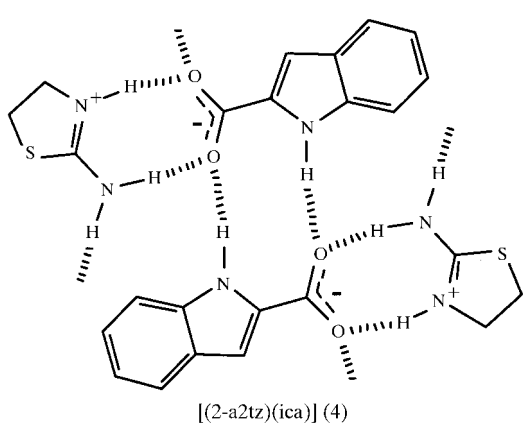


Fig. 2. Diagram showing the hydrogen-bonding interactions between associated ica molecules, in addition to the hydrogen-bonding network shown in Fig. 1(*f*), in the structure of [(2-a2tz)(ica)] (4).

3.2. *IR spectroscopy*

The principal mode of identification of the presence of proton transfer in compounds (1)–(9) is *via* IR spectroscopy (Williams & Fleming, 1973). Characteristic peaks which indicate this include medium to broad bands in the 2500–1800 cm^{-1} region due to N$^+$—H stretching frequencies and the presence of strong carboxylate antisymmetric and symmetric stretching frequencies between 1640–1550 and 1420–1300 cm^{-1}, respectively. Using these identifiers the spectra recorded for compounds (1)–(9) can be separated into two groups. The first group, containing compounds (1) and (3)–(8), display strong broad absorption peaks between 3500 and 2100 cm^{-1} and then weak broad bands at ∼2000–1700 cm^{-1}, due to N$^+$—H—O stretching frequencies. The second group, containing compounds (2) and (9), exhibit lesser intense peaks across the 3500–2700 cm^{-1} region but then show two broad medium intense bands at 2700–1750 cm^{-1}, again due to N$^+$—H—O stretching frequencies. The former pattern is usually only observed in proton-transfer adducts of 3-amino-1,2,4-triazole (Lynch, Dougall *et al.*, 1999), whereas the latter is generally observed in the spectra of both neutral and

Table 2. *Experimental details*

	(4)	(5)	(7)	(8)	(9)
Crystal data					
Chemical formula	$C_3H_7N_2S^+.C_9H_6NO_2^-$	$C_3H_7N_2S^+.C_6H_6NO_2^-$	$C_7H_7N_2S^+.C_9H_6NO_2^-$	$C_7H_7N_2S^+.C_6H_6NO_2^-$	$C_7H_7N_2S^+.C_5H_3O_2S^-$
Chemical formula weight	263.31	227.28	311.35	275.32	278.34
Cell setting	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	*Pbca*	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	8.771 (2)	11.9723	10.182 (4)	5.5561 (9)	9.162 (2)
b (Å)	13.344 (5)	12.5938 (10)	11.923 (2)	19.701 (3)	11.121 (3)
c (Å)	11.036 (2)	15.063 (2)	12.284 (6)	12.143 (2)	12.033 (2)
β (°)	108.314	90	107.23 (2)	100.263	104.388 (9)
V (Å^3)	1226.2 (6)	2271.1 (4)	1424.4 (9)	1307.9 (4)	1187.6 (5)
Z	4	8	4	4	4
D_x (Mg m^{-3})	1.426	1.329	1.452	1.398	1.557
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
θ range (°)	6–14	6–14	6–14	6–14	6–14
μ (mm^{-1})	0.262	0.27	0.238	0.249	0.442
Temperature (K)	298 (2)	298 (2)	298 (2)	298 (2)	293 (2)
Crystal form	Prism	Prism	Prism	Prism	Prism
Crystal size (mm)	0.5 × 0.3 × 0.24	0.5 × 0.4 × 0.18	0.6 × 0.2 × 0.18	0.5 × 0.3 × 0.1	0.48 × 0.24 × 0.2
Crystal colour	Colourless	Colourless	Colourless	Colourless	Colourless
Data collection					
Diffractometer	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4
Data collection method	2θ–ω scans	2θ–ω scans	2θ–ω scans	2θ–ω scans	2θ–ω scans
Absorption correction	ψ scan (*Xtal*3.2; Hall *et al.*, 1992)	None	ψ scan (*Xtal*3.2; Hall *et al.*, 1992)	ψ scan (*Xtal*3.2; Hall *et al.*, 1992)	ψ scan (*Xtal*3.2; Hall *et al.*, 1992)
T_{min}	0.857	–	0.899	0.870	0.768
T_{max}	0.939	–	0.998	0.998	0.915
No. of measured reflections	2295	2025	2641	2552	2334
No. of independent reflections	2147	1995	2494	2302	2197
No. of observed reflections	1400	1182	1504	1440	1538
Criterion for observed reflections	$F > 4\sigma(F)$	$F > 4\sigma(F)$	$F > 4\sigma(F)$	$F > 4\sigma(F)$	$F > 4\sigma(F)$
R_{int}	0.0183	0.0213	0.0758	0.0363	0.0233
θ_{max} (°)	24.97	24.97	24.94	24.97	26.21
Range of h, k, l	$0 \rightarrow h \rightarrow 10$ $0 \rightarrow k \rightarrow 15$ $-13 \rightarrow l \rightarrow 12$	$-6 \rightarrow h \rightarrow 14$ $-3 \rightarrow k \rightarrow 14$ $-9 \rightarrow l \rightarrow 17$	$0 \rightarrow h \rightarrow 12$ $0 \rightarrow k \rightarrow 14$ $-14 \rightarrow l \rightarrow 13$	$0 \rightarrow h \rightarrow 6$ $0 \rightarrow k \rightarrow 23$ $-14 \rightarrow l \rightarrow 14$	$0 \rightarrow h \rightarrow 11$ $0 \rightarrow k \rightarrow 13$ $-14 \rightarrow l \rightarrow 13$
Refinement					
Refinement on	F^2	F^2	F^2	F^2	F^2
$R[F^2>2\sigma(F^2)]$	0.0357	0.0366	0.0511	0.0381	0.0489
$wR(F^2)$	0.1011	0.1172	0.1620	0.1078	0.1560
S	1.002	0.997	0.936	0.991	1.051
No. of reflections used in refinement	2147	1995	2494	2302	2197
No. of parameters used	216	170	251	224	191
H-atom treatment	All H-atom parameters refined	Mixed	All H-atom parameters refined	All H-atom parameters refined	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0499P)^2 + 0.2456P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0574P)^2 + 0.5620P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.1084P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0544P)^2 + 0.2231P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0791P)^2 + 1.2898P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001	0.017	0	0	0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.172	0.164	0.266	0.223	0.502
$\Delta\rho_{min}$ (e Å^{-3})	−0.143	−0.162	−0.373	−0.274	−0.534
Extinction method	*SHELXL*	*SHELXL*	None	None	None
Extinction coefficient	0.0036 (14)	0.003 (1)	0	0	0

Table 2 (*cont.*)

	(4)	(5)	(7)	(8)	(9)
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Computer programs					
Data collection	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)
Cell refinement	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)	*MolEN* (Fair, 1990)
Data reduction	*Xtal*3.2 (Hall *et al.*, 1992)	*Xtal*3.2 (Hall *et al.*, 1992)	*Xtal*3.2 (Hall *et al.*, 1992)	*Xtal*3.2 (Hall *et al.*, 1992)	*Xtal*3.2 (Hall *et al.*, 1992)
Structure solution	*SHELXS*97 (Sheldrick, 1997)	*SHELXS*97 (Sheldrick, 1997)	*SHELXS*97 (Sheldrick, 1997)	*SHELXS*97 (Sheldrick, 1997)	*SHELXS*97 (Sheldrick, 1997)
Structure refinement	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)
Preparation of material for publication	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)	*SHELXL*97 (Sheldrick, 1997)

proton-transfer adducts of 2-aminopyridine and 2-aminopyrimidine (Lynch *et al.*, 1994). In all cases the carboxylate peaks occur towards the higher wavenumber range. One additional identifier not observed is a medium to weak amine salt ($N^+—H$) peak which is usually found between 1610 and 1670 cm^{-1}. Furthermore, an intense peak at ~1680 cm^{-1} is observed in the spectrum of compound (4) in addition to the antisymmetric peak <1640 cm^{-1}. Peaks in this region (1700–1680 cm^{-1}) have been previously observed for proton-transfer complexes which contain an $R_2^2(8)$ dimer similar to those in this series, but such peaks are yet to be assigned.

3.3. *Comments on the hydrogen-bonding interactions*

To date, the intermolecular non-hydrogen distances involved in the $R_2^2(8)$ interactions observed in one co-crystal of 2-aminopyridine (Lynch *et al.*, 1994), 23 co-crystals of 2-aminopyrimidine (Lynch *et al.*, 1997) and seven co-crystals of 3-amino-1,2,4-triazole (Lynch, Dougall *et al.*, 1999) have shown that this formation is slightly acentric with the average heterocyclic nitrogen/carboxylate oxygen distance being ~<2.7 Å, and the 2-amino nitrogen/carboxylate oxygen distance being slightly longer at ~2.9 Å. A survey of the equivalent distances for compounds (4), (5), (7)–(9) and other previously known carboxylic acid adducts of 2-aminothiazole derivatives, listed in Table 2, shows that in this series there is a decreased difference between the relevant non-H atoms in the $R_2^2(8)$ interaction with the two average distances being 2.690 (4) and 2.796 (4) Å, respectively, an average difference of ~0.1 Å. The lesser change, compared with the previous 2-aminoheterocyclic systems, occurs across the 2-amino nitrogen/carboxylate oxygen distance. There is no correlation between the decrease in this distance and the hydrogen-bonding associations involving the second amino proton. In this 2-aminothiazole series the second amino proton preferentially interacts with an adjacent carboxylate O atom, but some exceptions are observed where this proton associates with other hydrogen-bond accepting O or N atoms; the average distance [2.832 (4) Å] being slightly longer than the previously discussed 2-amino nitrogen/carboxylate oxygen distance. This networking interaction is not unique to this series, since nearly all of the above-listed 2-amino-heterocyclic adducts involve the second amino proton in the hydrogen-bonding network. Therefore, the average decrease in the N21—O22 distance must be due to the presence of the S atom. In this respect it would be interesting to compare similar distances in adducts of 2-aminooxazoles. Studies involving N3/N21-type receptor sites prove to be useful because intermolecular differences of >0.2 Å become significant in biological systems where accuracy is required to less than 0.2 Å (Neidle, 1994).

3.4. *Comments on proton transfer*

Proton transfer presents a wide variety of applications in the field of molecular biology. Therefore, it can be considered that the ability of hydrogen-bonding associations to facilitate proton transfer is an important chemical property. Just as the observation of second-harmonic generation from a powder sample can be used as supporting evidence in cases where non-centrosymmetric space groups are found (Kurtz & Perry, 1968), so too IR spectroscopy can be used as an identifier of proton-transfer complexes, particularly if the H atoms in a structure are difficult to locate. Thus it is always advantageous to have additional IR data when discussing the observation of proton transfer in these types of structures.

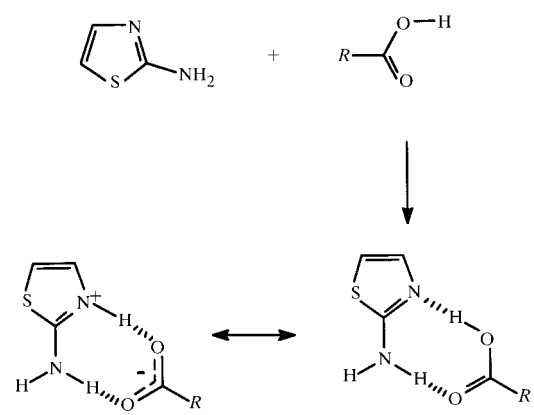
Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	U_{eq}
(4)				
S1*A*	0.19795 (9)	0.00838 (5)	0.63845 (7)	0.0583 (3)
N3*A*	0.1661 (3)	0.16112 (17)	0.76836 (18)	0.0496 (6)
C2*A*	0.1381 (3)	0.13027 (18)	0.6507 (2)	0.0436 (6)
N21*A*	0.0701 (3)	0.18557 (18)	0.5505 (2)	0.0532 (6)
C4*A*	0.2472 (5)	0.0918 (2)	0.8682 (3)	0.0635 (8)
C5*A*	0.2952 (5)	0.0013 (3)	0.8081 (3)	0.0687 (8)
N1*B*	0.1919 (3)	−0.07169 (15)	0.13668 (19)	0.0430 (5)
C2*B*	0.2073 (3)	−0.00759 (17)	0.23742 (19)	0.0387 (5)
C21*B*	0.1162 (3)	0.08695 (17)	0.2207 (2)	0.0412 (6)
O21*B*	0.1345 (2)	0.14099 (12)	0.31775 (14)	0.0502 (5)
O22*B*	0.0295 (2)	0.10985 (12)	0.10943 (15)	0.0527 (5)
C3*B*	0.3233 (3)	−0.04403 (19)	0.3415 (2)	0.0432 (6)
C4*B*	0.5028 (3)	−0.2028 (2)	0.3675 (2)	0.0484 (6)
C5*B*	0.5308 (3)	−0.2837 (2)	0.3011 (3)	0.0514 (7)
C6*B*	0.4424 (3)	−0.2977 (2)	0.1727 (3)	0.0516 (7)
C7*B*	0.3252 (3)	−0.23175 (19)	0.1086 (2)	0.0486 (6)
C8*B*	0.2957 (3)	−0.14973 (17)	0.1757 (2)	0.0408 (6)
C9*B*	0.3823 (3)	−0.13417 (17)	0.3060 (2)	0.0407 (6)
(5)				
S1*A*	0.10396 (7)	0.57877 (6)	0.13695 (6)	0.0765 (3)
C2*A*	0.1789 (2)	0.48668 (19)	0.19779 (16)	0.0487 (6)
N21*A*	0.1328 (2)	0.40105 (19)	0.23002 (17)	0.0578 (7)
N3*A*	0.28489 (19)	0.51026 (18)	0.20692 (15)	0.0544 (6)
C4*A*	0.3214 (3)	0.6114 (2)	0.1713 (2)	0.0620 (8)
C5*A*	0.2256 (3)	0.6608 (3)	0.1213 (2)	0.0766 (9)
N1*B*	−0.11048 (18)	0.15572 (17)	0.03712 (14)	0.0531 (6)
C11*B*	−0.2006 (3)	0.0842 (2)	0.0623 (2)	0.0782 (9)
C2*B*	−0.0787 (2)	0.2495 (2)	0.07766 (16)	0.0457 (6)
C21*B*	−0.1394 (2)	0.3023 (2)	0.15045 (17)	0.0476 (6)
O21*B*	−0.09063 (14)	0.37818 (15)	0.18912 (13)	0.0631 (6)
O22*B*	−0.23550 (15)	0.27121 (15)	0.16994 (13)	0.0683 (6)
C3*B*	0.0136 (2)	0.2864 (2)	0.03275 (18)	0.0549 (7)
C4*B*	0.0384 (3)	0.2150 (3)	−0.0356 (2)	0.0637 (8)
C5*B*	−0.0377 (3)	0.1368 (3)	−0.03099 (19)	0.0626 (8)
(7)				
S1*A*	0.5868 (1)	0.0512 (1)	0.7713 (1)	0.050 (1)
C2*A*	0.4924 (4)	0.1591 (3)	0.6908 (3)	0.042 (1)
N21*A*	0.4031 (4)	0.2180 (3)	0.7244 (3)	0.055 (1)
N3*A*	0.5209 (3)	0.1743 (3)	0.5927 (2)	0.041 (1)
C4*A*	0.6687 (4)	0.0969 (3)	0.4822 (3)	0.048 (1)
C5*A*	0.7659 (4)	0.0178 (4)	0.4807 (4)	0.059 (1)
C6*A*	0.8130 (5)	−0.0576 (4)	0.5696 (4)	0.062 (1)
C7*A*	0.7618 (4)	−0.0551 (3)	0.6628 (4)	0.054 (1)
C8*A*	0.6655 (4)	0.0256 (3)	0.6648 (3)	0.043 (1)
C9*A*	0.6186 (3)	0.1007 (3)	0.5747 (3)	0.039 (1)
N1*B*	0.8511 (3)	0.0547 (2)	1.0434 (3)	0.046 (1)
C2*B*	0.7533 (3)	−0.0009 (3)	1.0797 (3)	0.040 (1)
C21*B*	0.6908 (3)	−0.1046 (3)	1.0194 (3)	0.041 (1)
O21*B*	0.6067 (3)	−0.1589 (2)	1.0558 (2)	0.050 (1)
O22*B*	0.7264 (3)	−0.1292 (2)	0.9327 (2)	0.055 (1)
C3*B*	0.7375 (4)	0.0523 (3)	1.1721 (3)	0.041 (1)
C4*B*	0.8588 (4)	0.2304 (3)	1.2797 (3)	0.051 (1)
C5*B*	0.9547 (4)	0.3096 (3)	1.2754 (4)	0.056 (1)
C6*B*	1.0198 (4)	0.3093 (4)	1.1912 (4)	0.058 (1)
C7*B*	0.9939 (4)	0.2284 (3)	1.1090 (3)	0.053 (1)
C8*B*	0.8968 (3)	0.1465 (3)	1.1116 (3)	0.041 (1)
C9*B*	0.8271 (3)	0.1468 (3)	1.1954 (3)	0.040 (1)
(8)				
S1*A*	−0.00630 (14)	0.33873 (4)	0.48861 (6)	0.0386 (2)

Table 3 (*cont.*)

	x	*y*	*z*	U_{eq}
C2*A*	0.2038 (5)	0.29032 (14)	0.4325 (2)	0.0349 (6)
N21*A*	0.3906 (5)	0.26062 (14)	0.4945 (2)	0.0430 (6)
N3*A*	0.1550 (4)	0.28710 (12)	0.32170 (18)	0.0364 (6)
C4*A*	−0.1389 (6)	0.33343 (16)	0.1601 (2)	0.0437 (7)
C5*A*	−0.3439 (6)	0.37330 (16)	0.1296 (3)	0.0475 (8)
C6*A*	−0.4606 (6)	0.40344 (16)	0.2091 (3)	0.0465 (8)
C7*A*	−0.3724 (5)	0.39458 (15)	0.3216 (3)	0.0410 (7)
C8*A*	−0.1644 (5)	0.35563 (13)	0.3535 (2)	0.0330 (6)
C9*A*	−0.0507 (5)	0.32445 (13)	0.2729 (2)	0.0347 (6)
N1*B*	0.9112 (4)	0.08034 (12)	0.27295 (19)	0.0435 (6)
C11*B*	1.0778 (8)	0.0949 (3)	0.3773 (3)	0.0659 (11)
C2*B*	0.6982 (5)	0.11363 (13)	0.2273 (2)	0.0340 (6)
C21*B*	0.5973 (5)	0.17185 (14)	0.2800 (2)	0.0351 (6)
O21*B*	0.4199 (4)	0.20326 (10)	0.21895 (15)	0.0434 (5)
O22*B*	0.6802 (4)	0.18681 (11)	0.37872 (15)	0.0509 (6)
C3*B*	0.6062 (6)	0.08196 (14)	0.1284 (2)	0.0382 (7)
C4*B*	0.7644 (6)	0.02900 (16)	0.1129 (3)	0.0465 (8)
C5*B*	0.9498 (7)	0.02926 (16)	0.2023 (3)	0.0500 (8)
(9)				
S1*A*	0.06852 (10)	0.06403 (9)	0.75046 (8)	0.0429 (3)
C2*A*	−0.0521 (4)	0.1630 (3)	0.7869 (3)	0.0369 (8)
N21*A*	−0.1589 (4)	0.2112 (3)	0.7121 (3)	0.0475 (9)
N3*A*	−0.0232 (3)	0.1846 (3)	0.8991 (2)	0.0380 (7)
C4*A*	0.1475 (4)	0.1258 (4)	1.0809 (3)	0.0439 (9)
C5*A*	0.2660 (5)	0.0557 (4)	1.1290 (3)	0.0502 (10)
C6*A*	0.3297 (5)	−0.0150 (4)	1.0609 (4)	0.0506 (10)
C7*A*	0.2780 (4)	−0.0179 (4)	0.9433 (3)	0.0450 (9)
C8*A*	0.1591 (4)	0.0512 (3)	0.8954 (3)	0.0370 (8)
C9*A*	0.0939 (4)	0.1223 (3)	0.9636 (3)	0.0358 (8)
S1*B*	−0.43616 (13)	0.60626 (11)	0.84787 (12)	0.0681 (4)
C2*B*	−0.3181 (4)	0.5215 (3)	0.9447 (3)	0.0403 (8)
C21*B*	−0.2615 (4)	0.4083 (3)	0.9074 (3)	0.0409 (9)
O21*B*	−0.1768 (3)	0.3465 (2)	0.9826 (2)	0.0489 (7)
O22*B*	−0.3012 (3)	0.3811 (3)	0.8037 (2)	0.0558 (8)
C3*B*	−0.2836 (5)	0.5744 (3)	1.0561 (3)	0.0420 (9)
C4*B*	−0.3679 (6)	0.6800 (4)	1.0526 (4)	0.0639 (12)
C5*B*	−0.4508 (5)	0.7060 (4)	0.9494 (5)	0.0653 (13)



Proton-transfer complex

It has been suggested that a molecular description of the interaction of neurotransmitters such as histamine and their receptor binding sites is one of the major goals in pharmaceutical sciences and would also be helpful for

Table 4. *Distances and corresponding angles associated with the hydrogen-bonding geometries in compounds (4), (5), (7) and (9)–(11)*

Compound	N3*A*—H3*A*—O21*B*	N21*A*—H21*A*—O22*B*	N21*A*—H22*A*—O21*B*
[(2-a2tz)(ica)] (4)	2.728 (3) Å, 174 (3)° $x, \frac{1}{2}-y, \frac{1}{2}+z$	2.854 (3) Å, 170 (3)° $x, \frac{1}{2}-y, \frac{1}{2}+z$	2.861 (3) Å, 164 (3)°
[(2-a2tz)(mpca)] (5)	2.728 (3) Å, 176 (3)° $\frac{1}{2}+x, y, \frac{1}{2}-z$	2.726 (3) Å, 173 (3)° $\frac{1}{2}+x, y, \frac{1}{2}-z$	2.760 (3) Å, 173 (3)°
[(2-abtz)(ica)] (7)	2.751 (5) Å, 172 (3)° $1-x, \frac{1}{2}+y, \frac{3}{2}-z$	2.698 (5) Å, 170 (3)° $1-x, \frac{1}{2}+y, \frac{3}{2}-z$	2.820 (5) Å, 170 (3)° $1-x, -y, 2-z$
[(2-abtz)(mpca)] (8)	2.665 (4) Å, 174 (3)°	2.736 (4) Å, 174 (3)°	2.794 (4) Å, 168 (3)° $x, \frac{1}{2}-y, \frac{1}{2}+z$
[(2-abtz)(tca)] (9)	2.633 (5) Å, 175 (3)°	2.683 (5) Å, 167 (3)°	2.800 (5) Å, 172 (3)° $x, \frac{3}{2}-y, -\frac{1}{2}+z$
			N21—H22—O/N; reference
2-Aminothiazolium trichloroacetate	2.724 (3) Å	2.850 (3) Å	2.803 (3) Å; Kuz'mina & Struchkov (1984)
Diaminotetrahydrobenzothiazolium tartrate trihydrate	2.654 Å†	2.809 Å	2.815 Å; Schneider & Mierau (1987)
2-Aminobenzothiazolium 3,5-dinitrobenzoate hydrate	2.69 (1) Å	2.78 (1) Å	2.84 (1) Å; Lynch, Smith *et al.* (1998)
2-Aminobenzothiazole 3-aminobenzoic acid	2.613 (6) Å 2.653 (6) Å	2.922 (6) Å 2.904 (6) Å	2.891 (6) Å; Lynch, Smith *et al.* (1998) 3.002 (6) Å
2-Amino-2-thiazolinium 2-aminobenzoate	2.686 (5) Å 2.684 (5) Å	2.797 (5) Å 2.822 (5) Å	2.840 (5) Å; Lynch, Smith *et al.* (1998) 2.832 (5) Å
2-Amino-2-thiazolinium (2,4,5-trichlorophenoxy)acetate	2.756 (5) Å	2.773 (5) Å	2.763 (5) Å; Unpublished data
Average	2.690 (4) Å	2.796 (4) Å	2.832 (4) Å

† Calculated from CCDC data (file: FECZES).

the design of new therapeutics. Therefore, it is important to know how histamine interacts with the corresponding receptor binding sites. In this manner the aminothiazoles used in this series serve as useful molecular models. The thiazole N atom, N3, corresponds to the N^p nitrogen of the imidazole ring in histamine, which is supposed to interact with a hydrogen-bond donor site. The adjacent amino N atom, N21, corresponds to the N^t nitrogen, which is assumed to bind to a hydrogen-bond acceptor site. However, although a general rule governing the protonation of pyridine by carboxylic acids has been established for some time (Johnson & Rumon, 1965), no such indicator has been proposed for the occurrence of proton transfer in 2-aminopyridine-type complexes. The only 2-aminothiazole derivative adduct incorporating a carboxylic acid, but which is not a proton-transfer complex, is the 1:1 2-aminobenzothiazole 3-aminobenzoic acid adduct, which exhibits two unique pairs of molecules in the asymmetric unit (Lynch, Smith *et al.*, 1998). This is due to a difference in the hydrogen-bonding networks surrounding each molecular pair but, apart from this, there is nothing instantly outstanding in this structure which could explain why either molecular pair are neutral instead of being zwitterionic as in all of the other complexes listed in Table 4. As previously mentioned, all 3-amino-1,2,4-triazole and 2-aminopyridine adduct complexes involve proton transfer, whereas only four of the 16 2-aminopyrimidine complexes studied involve this process.

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